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Drug-induced QT interval prolongation: does ethnicity of the thorough QT study population matter?

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Inter-ethnic differences in drug responses have been well documented. Drug-induced QT interval prolongation is a major safety concern and therefore, regulatory authorities recommend a clinical thorough QT study (TQT) to investigate new drugs for their QT-prolonging potential. A positive study, determined by breach of a preset regulatory threshold, significantly influences late phase clinical trials by requiring intense ECG monitoring. A few studies that are currently available, although not statistically conclusive at present, question the assumption that ethnicity of the study population may not influence the outcome of a TQT study. Collective consideration of available pharmacogenetic and clinical information suggests that there may be inter-ethnic differences in QT-prolonging effects of drugs and that Caucasians may be more sensitive than other populations. The information also suggest s that (a) these differences may depend on the QT-prolonging potency of the drug and (b) exposure–response (E–R) analysis may be more sensitive than simple changes in QT_c interval in unmasking this difference. If the QT response in Caucasians is generally found to be more intense than in non-Caucasians, there may be significant regulatory implications for domestic acceptance of data from a TQT study conducted in foreign populations. However, each drug will warrant an individual consideration when extrapolating the results of a TQT studyfrom one ethnic population to another and the ultimate clinical relevance of any difference. Further adequately designed and powered studies, investigating the pharmacologic properties and E–R relationships of additional drugs with different potencies, are needed in Caucasians, Oriental/Asian and African populations before firm conclusions can be drawn.

Introduction

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) consists principally of the regulatory and industry members of the three major pharmaceutical regions of the world, namely the European Union, United States and Japan. By affiliation, it has in practice a much broader, almost universal, constituency. ICH is mandated with developing guidelines to harmonize global drug development and thus facilitate availability of new medicines efficiently. A key consideration for global drug development and registration therefore is the acceptability of foreign clinical data by the three ICH regions.

Drug-induced prolongation of QT interval of the surface electrocardiogram (ECG), and the associated risk of potentially fatal pro-arrhythmias, is a major safety issue. In order to address this safety concern pro-actively, regulatory authorities, under the auspices of ICH, adopted in May 2005 two guidelines (ICH S7B and ICH E14) [1, 2]. ICH S7B is concerned with non-clinical studies and promotes a concept of integrated risk assessment based on the chemical and pharmacological class of the drug together with data from two core studies, an *in vitro* IKr assay and an *in vivo* study in a suitable animal species [1]. ICH E14 is concerned with clinical investigation of the effect of drugs on QT interval [2]. Its focus is a specific 'thorough QT' (TQT) study, typically conducted in healthy volunteers, as the

primary method for evaluating the potential effect of non-cardiac agents on cardiac repolarization during drug development.

Without being too prescriptive, ICH E14 provides helpful and detailed guidance on the design and analysis of a TQT study. The variable most frequently used to study the QT-effect of a drug is either the maximum increase from baseline in heart rate corrected QT interval (ΔQT_c) or maximum time-matched placebo-adjusted increase in ΔQT_c ($\Delta\Delta QT_c$). Correction for heart rate is most frequently made by any one or more of the four formulae in common use, namely Bazett correction (QT_cB), Fridericia correction (QT_cF), population-specific correction (QT_cP) or individual subject-specific correction (QT_cI). QT_cB interval is the most and QT_cI interval is the least susceptible to heart rate changes. As proposed in ICH E14, the threshold level of regulatory concern is set at a mean $\Delta\Delta QT_c$ effect of about 5 ms, as evidenced by a 10 ms upper bound of the 95% confidence interval (CI) around the mean. The nominal determination of a drug as a potential QT-prolonger from the results of a TQT study is independent of whether the above threshold is breached at therapeutic or the supratherapeutic dose or at one time point or more following its administration. If a TQT study is determined to be positive because this threshold is breached, it does not necessarily mean that the drug is pro-arrhythmic but it does indicate the need for more intensive monitoring of the ECG in the patient populations in later phase clinical trials to assess the clinical risk of pro-arrhythmia. Clearly, the determination of a TQT study as either positive or negative has major impact on subsequent drug development.

When ICH E14 was first adopted in 2005, it was assumed that the results of a TQT study would not be affected by ethnic factors but it was acknowledged that the data were limited at that time. This paper summarizes the currently available data which suggest that ethnicity may be an important issue and calls for a debate on whether ethnicity of the population enrolled in a TQT deserves greater attention than given hitherto.

Why the regulatory concerns on QT prolongation?

Currently, a major focus of regulatory authorities is the cardiac safety of new and many established drugs, particularly their potential to prolong the QT interval. IKr is the principal repolarizing current carried by the rapid component of delayed rectifier potassium channel. The vast majority of the drugs prolong QT interval by inhibition of the *KCNH2*-encoded hERG (human ether-a-go-go related gene) subunit of the IKr channel. An extensive literature search by the author in 2008 identified just over 160 drugs capable of prolonging QT interval. A partial list of these drugs, to illustrate the wide range of therapeutic, pharmacologic or chemical classes involved, is shown in Table 1.

Table 1

A selection of drug classes involved in drug-induced QT interval prolongation*

Pharmaco-therapeutic or chemical drug class	Reported representative examples
α-adrenoreceptor antagonists	Alfuzosin, indoramin, ketanserin, lofexidine
Anaesthetics	Desflurane, enflurane, halothane, isoflurane, propofol, sevoflurane
Analgesics and opiate agonists	Levacetylmethadone, methadone, oxycodone, propoxyphene
Anti-anginal drugs	Lidoflazine, prenylamine, ranolazine, (terodiline)
Antiarrhythmic drugs	Ajmaline, almokalant, amiodarone, aprindine, azimilide, bepridil, disopyramide, dofetilide, dronedarone, ibutilide, lorcainide, nifekalant, procainamide, quinidine, semitilide, sotalol, tedisamil, terikalant
Antibacterials	Azithromycin, clarithromycin, clindamycin, erythromycin, roxithromycin, spiramycin, telithromycin
Antidepressants	Amitriptyline, citalopram, desipramine, fluoxetine, nortriptyline, protriptyline, trazodone, venlafaxine
Antifungal agents	Fluconazole, ketoconazole, posaconazole, voriconazole
Antihistamines	Astemizole, diphenhydramine, hydroxyzine, mizolastine, terfenadine
Antimalarials	Choloroquine, halofantrine
Antitussive agent	Clobutinol
Cytotoxic drugs	Aclarubicin, acodazole, arsenic trioxide, depsipeptide, vorinostat
Fluoroquinolones	Ciprofloxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, ofloxacin, sparfloxacin
Lipid lowering agent	Probucol
Neuroleptic agents	Chlorpromazine, droperidol, haloperidol, melperone, mesoridazine, pimozide, quetiapine, risperidone, sertindole, thioridazine, ziprasidone
Non-nucleoside reverse transcriptase inhibitor	Efavirenz
Oestrogen receptor modulators	Tamoxifen, toremifene,
Phosphodiesterase inhibitors	Sildenafil, tadalafil, vardenafil
Protease inhibitors	Atazanavir, nelfinavir, saquinavir
Serotonin antagonists	Cisapride, dolasetron, domperidone, ondansetron
Tyrosine kinase inhibitors	Dasatinib, lapatinib, nilotinib, sunitinib, vandetanib

*This list is alphabetical in order and not all-inclusive.

The list has since continued to increase and the number of such drugs now exceeds 200. When prolonged excessively, or in the presence of appropriate risk factors, prolonged QT interval leads to a potentially fatal ventricular tachyarrhythmia known as torsade de pointes (TdP). TdP subsequently degenerates into ventricular fibrillation (VF) in about 15–20% of cases [3] and, not uncommonly, cardiac arrest and sudden death may be the outcome. Although it is very rare for QT interval prolongation to degenerate into TdP, the overall mortality from TdP is of the order of

Table 2

Drugs withdrawn from the market as a result of their QT-liability and/or TdP

Drug	Therapeutic class	Year of withdrawal
Prenylamine	Anti-anginal	1988
Lidoflazine	Anti-anginal	1989
Terodiline	Anti-anginal/Urinary incontinence	1991
Terfenadine	Antihistamine	1998
Sertindole*	Antipsychotic	1998
Astemizole	Antihistamine	1999
Grepafloxacin	Antibiotic	1999
Cisapride	Gastric prokinetic	2000
Droperidol	Tranquillizer/analgesic	2001
Levacetylmethadol	Methadone substitution	2001
Dofetilide‡	Atrial fibrillation	2004
Thioridazine	Antipsychotic	2005
Clobutinol	Antitussive	2007
Dextropropoxyphene†	Opioid analgesic	2009

*Re-introduced later following re-evaluation of risk–benefit. †In addition to QT-liability, safety in overdose was also an issue. ‡Withdrawn by the sponsor for commercial reasons.

10–20% [4–7]. Consequently, although the incidence of TdP in association with a given drug may be very low, it adversely affects the risk : benefit ratio of the drug, especially when the indication is a relatively benign and often self-limiting condition. Regulatory authorities react by either withdrawing the drug from the market or placing severe prescribing restriction on its use [8].

In terms of drug withdrawals from the market, QT interval prolongation, with or without the associated pro-arrhythmia, ranks only second to drug-induced hepatotoxicity as a cause for their withdrawal (26% and 37%, respectively during the period 1990–2006) [9]. Prenylamine and lidoflazine, both anti-anginal agents, were withdrawn from the market in 1988 and 1989, respectively because of their torsadogenic potential. Of the 56 drugs withdrawn from the major markets of the world during the period from 1990 to February 2012, 12 (21.4%) were withdrawn due to their potential to prolong QT interval and/or induce TdP (Table 2). Regulatory approval for marketing authorizations has been delayed or denied to a number of new drugs, and prescribing restrictions have been placed on countless new and established medicines, as a result of their QT liability. In addition, regulatory authorities now routinely include substantial descriptive data on the effect of new drugs on QT interval in their prescribing information.

Inter-ethnic differences in drug response

Inter-ethnic differences in drug disposition and responses are well known and have been previously reviewed by a number of authors [10–12]. These differences vary in their magnitude but the regulatory implication of this reached its climax on 23 June 2005 with the approval by the US Food and Drug Administration (FDA) of BiDil, a proprietary fixed-dose combination of 20 mg isosorbide dinitrate and 37.5 mg hydralazine hydrochloride, for use in cardiac failure. A series of efficacy studies revealed that although there was no overall significant difference in mortality between placebo and BiDil in an ethnically-mixed population, there was a statistically significant reduction in all-cause mortality and risk of first hospitalization for heart failure in self-identified Black patients. Therefore, although the decision was controversial [13, 14], the combination was approved for use in the treatment of heart failure as an adjunct to standard therapy in self-identified Black patients. BiDil represents the first drug to be approved for use in a specific racial or ethnic group.

There are similar marked inter-ethnic differences in the safety of some drugs. Ibufenac and clioquinol are now almost classical examples of this difference. Ibufenac, a non-steroidal anti-inflammatory drug that preceded ibuprofen, was introduced to the UK market in April 1966 and withdrawn from clinical use in February 1968 because of serious and frequent hepatotoxicity. Although this complication was relatively frequently observed in the UK, it was almost unknown in Japan [15]. Indeed, the drug continued to be available in Japan for some time after its withdrawal from the UK market and was withdrawn for reasons of commercial viability. Clioquinol, an anti-diarrhoeal agent, was first introduced in Japan in 1929. During the 1950s, reports of clioquinol-induced neuropathy began to appear. Soon, physicians were reporting the appearance in Japan of a new syndrome called subacute myelo-optic neuropathy (SMON) in association with clioquinol, with the number reaching some 10 000 cases of SMON in Japan during 1957 to 1970 [16]. However, there were only a few cases of clioquinol-induced neuropathy but none of SMON reported in the UK and despite wide use of clioquinol, there was only a handful of reports of SMON from other parts of the world [17, 18]. No universally agreed explanation has emerged to account for this epidemic in Japan, although chronic use with excessive doses is one potential explanation.

Regulatory authorities have been frustrated by under-representation of important patient populations in clinical trials, such as adolescents, elderly, females and ethnic minorities. An analysis of 452 applications for marketing authorizations reviewed by the European Committee for Proprietary Medicinal Products for Human Use (CHMP) during 2005–2009 revealed that of the 595 580 patients included, 38.8% of the patients came from EU/EEA/EFTA countries, 35.2% from North America, 7.8% from Middle East/Asia/Pacific, 3.0% from Africa and 15.2% from the rest of the world [19]. It is of course recognized that within these geographic regions, there is considerable ethnic mix of the population. For example, according to the US 2000

census, the US population consisted of 69.1% Whites, 12.5% Hispanics, 12.1% Black or African-American and 3.6% Asians [20]. There are no recent data available but a retrospective analysis of racial and ethnic group participation in clinical trials and race-related labelling of 185 new molecular entities approved during a 5 year period (1995–1999) by the FDA found that of the ethnic minorities there, African Americans participated in trials to the greatest extent. However, their participation steadily declined from 12% in 1995 to 6% in 1999. Labelling of 84 (45%) products contained some statement about race, although only 15 (8%) of these included 18 race-related differences. Of these 18 statements, nine (50%) related to pharmacokinetics, seven (39%) to efficacy and two (11%) to safety. Only one product label recommended a change in dosage based on racial differences [21]. Another study found that although the total number of trial participants increased during the study period, the representation of ethnic minorities decreased [22]. Despite the very low number of non-White Caucasian patients randomized into clinical trials, sponsors expect to extrapolate the safety and efficacy data from one ethnic population to another. Although these authorities now require adequate representation of all relevant subgroups of target population to be studied in clinical trials, there is frequently a substantial imbalance in representation of various ethnic minorities, thus frustrating the intended objectives of analyses of efficacy and safety by various demographic subgroups of the population. Increasingly, drug development programmes now are undertaken at a global level. The objectives are not only to reduce the costs and expedite the drug development process but evidently also to address issues related to inter-ethnic differences in prescribing and drug response.

Regulatory authorities have responded to the challenges arising from these developments by promulgating a number of guidelines that recommend sponsors of new drugs to explore the role of genetic and non-genetic variations in differences in drug response between individuals and between ethnic populations (Table 3). When evaluating new drugs, therefore, these authorities are now increasingly directing their attention to addressing issues that may arise from genetic or ethnic heterogeneity of the trial population and the target patient population. Among the major drug safety concerns today are drug-induced hepatotoxicity and QT interval prolongation with TdP. Female gender is reportedly an important risk factor for both these toxic effects [4, 23–27]. However, the role of ethnicity has not received the attention it deserves.

Ethnicity and drug-induced QT prolongation

Before considering any potential differences in drug-induced effects, it is worth considering whether there are inter-ethnic differences in baseline, drug-free QT_c intervals.

Table 3

Regulatory guidance documents relevant to analysis by ethnicity

Year	Guidance	Reference
1993	FDA: *New Drug Evaluation Guidance Document: Refusal to File*,	[65]
1994	*ICH E4: Dose–response information to support drug registration*	[66]
1998	FDA: *Demographic Rule*	[67]
1998	ICH E5: *Note for Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data.*	[68]
2004	ICH E2E: *Pharmacovigilance Planning*	[69]
2005	FDA: *Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials*	[70]
2009	EMA: *Reflection paper on the extrapolation of results from clinical trials conducted outside the EU to the EU-population*	[71]

Unfortunately, the data are very sparse. A PubMed search in July 2012, combining the terms 'ethnic' or 'ethnicity' and 'QT', retrieved only 86 citations, most of which were irrelevant to the subject matter of this paper; namely healthy volunteers which is the population typically studied in a TQT study. Even studies that have examined ethnic differences in the prevalence of variant potassium channels do not provide baseline ECG data of the subjects studied [28]. Large population-based studies that have reported marked age- and sex-related variations in the reference ranges have not addressed the issue of ethnicity [29].

What few data are available suggest that there are no inter-ethnic differences in baseline QT_c intervals [30, 31]. The Women's Health Initiative study concluded that the comparison of the mean values and upper and lower normal standards established in the different ethnic groups revealed that the racial differences can be ignored, except that the mean adjusted QT values were 6 to 7 ms greater and the upper 98th and 95th percentile limits approximately 10 ms greater in Asian women than in the other racial groups [32]. An association between a single nucleotide polymorphism (SNP), rs13017846, which maps to near SLC8A1 (sodium/calcium exchanger 1 precursor), and the QT interval has been reported recently. The frequency of this SNP varies widely between ethnicities (0.053 in Europeans, 0.080 in Africans and 0.500 in Asians/Orientals [33] and may give rise to inter-ethnic differences in QT interval.

Although there were hardly any data when ICH E14 was adopted in 2005, clinical data are now gradually emerging

to raise questions regarding the initial assumption that ethnicity is not expected to influence the response to a QT-prolonging drug, and therefore, the results of a TQT study. This evidence is at present sparse but sufficiently suggestive as to warrant formal studies. It should be emphasized that what evidence exists is derived from studies that were not adequately powered to detect these differences in statistical terms, given the anticipated effect size (potency of the QT prolonging drug). In an analysis of 20 TQT studies by Florian *et al*. Black subjects constituted on average 10.2% and Asians 6.6% of the entire study population of 985 subjects (of whom females accounted for a 42.8%) [34]. In a very recent study aimed at 're-evaluation of moxifloxacin pharmacokinetics and their direct effect on the QT interval', there was a total of 99 subjects of whom 78 were Caucasian, nine were Black, three were Asian and nine were multiracial [35]. Consequently, many such studies do not reveal statistically significant inter-ethnic differences but the trends appear consistent. The Japanese authority (Pharmaceutical and Medical Devices Agency) requires the sponsor of a drug to provide a proper explanation of why foreign TQT data is being used for assessment of proarrhythmia risk in the Japanese and to justify extrapolation of TQT data from foreign populations to the Japanese population, bearing in mind the anticipated (differences or similarities in) exposure and influence of other extrinsic factors in the Japanese population. In some cases of uncertainty, the Japanese authority may consider the need for an additional TQT study in the local population.

Before proceeding any further, it may be helpful to distinguish certain terms used in this paper. QT liability is a term that refers to the intrinsic property of a drug whereas QT susceptibility may be an appropriate term to describe exposure-related diathesis of a patient or a population, e.g. the QT effect of (S)-methadone in CYP2B6 poor metabolizers [36]. In contrast, QT sensitivity better describes a patient or a population that displays an exaggerated QT response at normal or even subnormal exposures, e.g. patients with hypokalaemia or harbouring mutations of cardiac ion channels [37, 38]. Although the precise mechanistic explanation remains elusive, the key pharmacological basis that likely underpins potential inter-ethnic differences in QT-susceptibility may be summarized as follows:

- There are significant inter-ethnic differences in the frequency of variant alleles of genes (e.g. *CYP2D6*, *CYP2C19*, *CYP2C9*) that encode for drug metabolizing enzymes, resulting in inter-ethnic differences in metabolism of their substrates [20, 39–42]. Relatively few QT-prolonging drugs are metabolized predominantly by CYP2C19 and hardly any by CYP2C9, Apart from CYP3A4, a large number of QT-prolonging drugs are predominantly metabolized by the highly polymorphic CYP2D6 and the frequency of variant alleles of CYP2D6 that result in impaired drug metabolism (and therefore, increased plasma concentrations of these drugs) is higher among white Caucasians compared with their Oriental counterparts, potentially giving rise to QT-susceptibility.
- There are marked inter-ethnic differences in the frequency of variant alleles of *KCNH2*, *KCNE2*, *KCNQ1*, *KCNE1* and *SCN5A* genes, encoding for cardiac ion channels, with some alleles being population-specific [28, 43–45]. Most drugs that prolong QT interval do so by inhibiting the *KCNH2*-expressed α-subunit (hERG) of the IKr channel. Subjects who carry these mutations have diminished repolarization reserve and are QT-sensitive. The frequency of variant *KCNH2* alleles that results in sensitivity to drug-induced QT interval prolongation is higher among White Caucasians.
- Some variant alleles, encoding for drug metabolizing enzymes (for example, *CYP2D6*10*) or hERG potassium channels (for example, R1047L and to a lesser extent, K897T), are for all intent and purposes population-specific [28, 39]. Data indicate that ethnic differences in the clinical expression of LQTS can be attributed to the differences in frequencies of the specific mutations within the two populations [46].
- It has been demonstrated recently that common variations in the NOS1AP gene are associated with a significant increase in the risk of drug-induced long QT syndrome [47]. At present, there is not sufficient information on the significance of this finding in terms of inter-ethnic differences in QT-sensitivity.
- Results from a few clinical studies that are available at present suggest the possibility of inter-ethnic differences in response to QT-prolonging drugs.

These clinical studies are further discussed below and their results seem to suggest that the likelihood of detecting inter-ethnic differences in QT response depends on the potency of the QT-prolonging effect of the drug concerned. As the intensity of effect on QT_c interval becomes milder, it can become progressively difficult to determine any differences between two subgroups. In an extreme example of a drug that is devoid of any QT effect, there is no difference to detect.

Quinidine – a potent QT-prolonger

Results from two studies with quinidine, a potent QT-prolonging agent, have been consistent in showing an inter-ethnic difference in QT sensitivity (Table 4). In the first study published as early as 1982, prolongation of the QT_c interval from baseline following a single 400 mg oral dose of quinidine was greater in the healthy White subjects (n = 7) compared with their Nigerian counterparts (n = 7), although the Nigerians had higher plasma quinidine concentrations [48]. Baseline QT_c intervals were marginally but not statistically shorter in the Caucasians than in the Nigerians (401 $\pm$ 21 ms *vs.* 414 $\pm$ 33 ms). The increase in QT_c interval from baseline was 43 ms in Caucasians and

Table 4

Changes in QT_c interval (ms) from baseline in populations of different ethnicities

Drug # hERG IC_{50}	QT_c	Caucasians	Orientals	Africans	Reference
Quinidine **0.41 μM**	ΔQT_cB (oral)	43		30	[48]
	ΔQT_cB (i.v.)	~120 (males) ~125 (females)	~110 (males) ~80 (females)		[49] [49]
Moxifloxacin **90 μM**	$\Delta\Delta QT_cI$ (i.v.)	15.6		15.3	[51]
	$\Delta\Delta QT_cF$ (oral)	12.3 ~11.7	 ~10	 ~7.5	[53] [34]
Levofloxacin **460 μM**	$\Delta\Delta QT_cF$ (oral)	7.1	4.5*		[58]

*Value predicted at the same concentration from PK/PD modelling. #One or mean of several values from the published literature. ~Values deduced from the diagrams published in the reference cited. i.v., intravenous infusion.

30 ms in Nigerians. At 0.7 μg ml^{-1} of plasma quinidine concentration, the mean (SD) ΔQT_c values were 27 (15) ms in Caucasians and 16 (7) ms in Nigerians. From these data, the present author computed the exposure–response (E–R) slopes of approximately 0.03857 ms ng^{-1} ml^{-1} in Caucasians and 0.02286 ms ng^{-1} ml^{-1} in Nigerians. None of these differences was statistically significant. A major drawback of this study is that only single ECG traces seem to have been recorded at each time point. QT intervals were typically measured over six cardiac cycles in a limited number of leads only and the ECGs were read at two different sites, thus potentially introducing a bias from technical variability and natural changes in QT_c interval. In the second study, published much later in 2007, Caucasian (n = 13) and Korean (n = 24) subjects were administered an intravenous infusion of 4 mg kg^{-1} quinidine or saline over a 20 min period in a crossover design, the two periods being separated by 1 month [49]. This was a very carefully planned and conducted study even to the extent of taking into account the menstrual phase of female volunteers to minimize any possible potential contribution of changing pattern of sex hormones. Although this study was also conducted at two sites (US and Korea), the ECGs from both the sites were analyzed and read blindly by a trained technician at only one centre (US). The baseline QT_c intervals in the two populations were comparable (423 ± 7 ms in Koreans and 438 ± 15 ms in Caucasians). The change in the QT_c (ΔQT_c) was calculated as the difference between the QT_c intervals of subjects after saline administration *vs.* that after quinidine. Since QT_c interval shows circadian variation and the two study periods were separated by 1 month, this seems a reasonable approach to determine a drug effect. There were no statistical differences in the pharmacokinetic profiles of quinidine between the two ethnic groups. However, QT_c interval values in the Caucasians were higher than those in the Koreans at the same quinidine concentrations, although these differences were not statistically significant. The reported scatter plots of the relationship between plasma quinidine concentration and the QT_c value observed after intravenous infusion of quinidine to the study cohorts show a more pronounced sensitivity of the Caucasians. The difference between the two ethnic groups was especially marked in female subjects and at higher quinidine concentrations.

Moxifloxacin – a mild to moderate QT-prolonger

Since moxifloxacin, a mild to moderate QT prolonger, is widely used as a positive control in TQT studies to establish assay sensitivity, a vast amount of data has accumulated on its QT-prolonging properties. The data on its QT-prolonging effects in different populations are not as consistent as they are with quinidine.

Two studies with moxifloxacin suggest lack of any inter-ethnic difference in its QT sensitivity. Following a study of 36 healthy volunteers, stratified as Hispanics or non-Hispanics, Wheeler *et al*. [50] reported that the observed maximum ΔQT_cF in response to moxifloxacin was 17.4 ms at 3.5 h post-dose for Hispanics and 15.2 ms at 3 h post-dose for non-Hispanics, although this difference was not statistically significant. Since there is no further information on the ethnic background of non-Hispanics, it is difficult to comment further on the significance of this study. However, Malik *et al*. [51] assessed baseline and placebo-controlled QT_c changes at 126 data points before, during and after an intravenous infusion of 400 mg moxifloxacin over 1 h in 44 healthy participants (including 22 Africans, 16 whites and 6 'others'). Intravenous placebo was administered as physiologic saline solution with the two treatments separated by sufficient washout. Measured QT intervals were corrected by applying individually-derived correction formula. In each participant, the time sequences of QT_c readings on moxifloxacin and placebo were time matched, synchronizing the moment of the end of drug

Table 5

Concentration-QT response slopes in populations of different ethnicities (ms ng^{-1} ml^{-1})

Drug # hERG IC_{50}	Type of QT_c	Caucasians	Orientals	Africans	Reference
Quinidine **0.41 μM**	QT_cB	0.03857		0.02286	[48]
Moxifloxacin **90 μM**	Various	Mean of 20 studies = 0.0031 (range 0.0016 to 0.0048) Higher slopes reported in four studies with higher proportion on Caucasians Lower slopes reported in seven studies with lower proportion of Caucasians			[34]
	QT_cI	0.003571			[57]
Levofloxacin **460 μM**	QT_cF	0.0004920	0.0003640		[58]

#One or mean of several values from the published literature.

delivery, and the differences between readings on moxifloxacin and on placebo (ΔQT_c values) were studied in the total population and in gender-, race-, and age-defined subpopulations. At each time point, the mean and 95% CIs of the ΔQT_c values were calculated assuming normal distribution. There was no difference in QT-prolonging effect related to gender, ethnicity or age. The post-infusion peak $\Delta\Delta QT_cI$ values were 15.6 ± 6.6 ms in Whites and 15.3 ± 5.3 ms in Africans and the maximum plasma concentrations (averaged during 2–15 min post-infusion) were 3.5 ± 0.7 and 3.2 ± 0.7 μg ml^{-1}, respectively. It may be noted that this study found that $\Delta\Delta QT_c$ values were higher in subjects with lower body mass index compared with those with a higher body mass index, recommending that obese participants should be excluded from TQT studies. In contrast, a more recent study in a much larger sample size reported that ibutilide-induced QT interval prolongation was greater in overweight and obese subjects than in subjects with normal or low body mass index [52].

Yan *et al*. have reported that $\Delta\Delta QT_cF$ due to moxifloxacin was 12.3 (90% CI 11.3, 13.3) ms in a pooled analysis of 14 crossover TQT studies [53], enrolling mostly the White Caucasians whereas in a TQT study of telbivudine in 53 subjects, all of whom were Hispanics, the $\Delta\Delta QT_cF$ for moxifloxacin was lower at 10.0 (90% CI 6.9, 13.1) ms [54]. Florian *et al*. have also recently reported on the effect of moxifloxacin on QT_cF interval by gender and race [34]. Data available from 20 TQT studies submitted to the FDA were analyzed. The dataset included 788 Caucasians, 105 Blacks and 72 Asians. E–R analysis, using baseline- and placebo-adjusted QT_cF ($\Delta\Delta QT_cF$), revealed an estimated mean slope of 0.0031 ms ng^{-1} ml^{-1} for moxifloxacin effect across these 20 studies. However, the reported wide range of this slope (0.0016 to 0.0048 ms ng^{-1} ml^{-1}) emphasizes the wide inter-individual variability in QT response (Table 5). Although the time *vs*. $\Delta\Delta QT_cF$ profile did not reveal any statistically significant inter-ethnic difference, the confidence limits for this comparison were wide. These investigators did not report any further subgroup analysis of the data by ethnicity but a visual inspection of the time *vs*. $\Delta\Delta QT_cF$ profile reported by these investigators shows that the QT effect of moxifloxacin is greater in Caucasians than in the other two populations. This difference could be related to simply a difference in exposure (pharmacokinetic susceptibility) or to a difference in E–R relationship (pharmacodynamic sensitivity). The former seems unlikely since the dose is fixed at a 400 mg single dose and there are no reasons to suspect, or data to support, ethnic differences in exposure. In one study, even over-encapsulation of moxifloxacin did not alter its peak or total systemic exposures [55]. The magnitude of correlation between population peak concentrations of moxifloxacin and the largest effect on $\Delta\Delta QT_cF$ reported by Yan *et al*. [53] also rules out an entirely exposure-based explanation for the magnitude of the inter-ethnic differences in $\Delta\Delta QT_cF$ observed in the analysis reported by Florian *et al*. [34]. Importantly, furthermore, a detailed examination of the data reported by Florian *et al*. [34] shows that the high E–R slopes were associated with four studies which enrolled a mean of 90% Caucasians whereas the low E–R slopes were associated with seven studies which enrolled a mean of 62% Caucasians. The highest slope was observed in a study that enrolled 90% Caucasians and the lowest in a study that enrolled only 52% Caucasians. These statistics suggest that ethnicity has an influence on QT response to moxifloxacin.

Levofloxacin – a mild QT-prolonger

Levofloxacin, compared with moxifloxacin, is less potent in prolonging QT interval [56, 57]. The $\Delta\Delta QT_cI$ effects of 400 mg moxifloxacin and 1500 mg levofloxacin in Caucasians were 13.19 (95% CI 11.21, 15.17) ms and 7.44 (95% CI 5.47, 9.42) ms, respectively [57]. It is evident that the 95% upper bound of the mean effect of levofloxacin in Caucasians (9.42 ms) is close to the 10 ms threshold of regulatory concern. The inter-ethnic difference in the effect of levofloxacin is consistent with the greater sensitivity of Caucasians to the QT-prolonging activity quinidine and moxifloxacin discussed above. Sugiyama *et al*. [58] have

reported on a retrospective analysis of two studies with levofloxacin, one was a formal TQT study [57] whereas the other was of similar quality, evaluating the effect of levofloxacin on the QT interval in Caucasian and Japanese subjects. The Japanese subjects, dosed with 500 mg levofloxacin intravenously, demonstrated a mean $\Delta\Delta QT_cF$ of 3.4 ms (upper bound of one-sided 95% CI was 5.2 ms) whereas the Caucasian subjects who received 1000 mg and 1500 mg doses of levofloxacin orally demonstrated a mean $\Delta\Delta QT_cF$ of 4.7 and 7.1 ms, respectively (upper bounds of one-sided 95% CI were 7.0 and 9.1 ms, respectively). Although these observed dose-dependent effects of levofloxacin may appear at first glance to exclude an ethnic difference, E–R analyses in the two populations revealed a difference in sensitivity. The slopes of levofloxacin effect on $\Delta\Delta QT_cF$ were 0.000364 (90% CI 0.000189, 0.000539) ms ng^{-1} ml^{-1} in the Japanese and 0.000492 (90% CI 0.000380, 0.000604) ms ng^{-1} ml^{-1} in the Caucasians (Table 5). Although this difference in the two slopes is not statistically significant, the slope for Japanese subjects is approximately only 74% of that observed in Caucasians, suggesting that Caucasian subjects are more sensitive to the QT-prolonging effect of levofloxacin. In terms of equivalency or lack of equivalency of effect, one could apply the criteria typically applied to assess bioequivalence to appreciate this difference in slopes. Sugiyama *et al*. [58] acknowledge that although the difference between the two populations is not statistically significant in the clinically relevant plasma concentration range investigated in this analysis, the trend suggests that Caucasian subjects are more sensitive, in agreement with Shin *et al*. [49]. Analysis of the QT effect of levofloxacin by analyzing $\Delta\Delta QT_c$ and by E–R relationship in different populations reveals the superior value of analysis by E–R relationship in studying population differences in sensitivity. Sugiyama *et al*. [58] have not reported on moxifloxacin E–R slope in the Japanese, but this slope was found to be approximately 0.003571 ms ng^{-1} ml^{-1} in the Caucasian arm of the study [57], a value comparable with that reported by Florian *et al*. [34].

Significance of ethnicity of population enrolled in a TQT study

Collective assessment of the above preliminary data, together with known pharmacokinetic and pharmacodynamic differences between populations suggest that for some QT-prolonging drugs, the ethnicity of the population enrolled in a TQT study could prove to be as important as other aspects of study design, conduct and analysis in determination of the TQT study as positive or negative, and therefore, the consequences for further development of the drug. From a regulatory perspective, a TQT study is determined as positive or negative depending on whether or not the effect of the drug on QT_c interval breaches the preset threshold of regulatory concern. For drugs such as quinidine which are potent QT-prolongers, the effects in two ethnic populations in the TQT study may be different but sufficiently intense that ethnicity is unlikely to be relevant in terms of determining the TQT as positive. For drugs which have minimal or no effect on QT_c interval, ethnicity of the TQT study population may also be irrelevant. However, ethnicity may be important for the remainder. For example, in the levofloxacin studies described above, the 95% upper bound of the $\Delta\Delta QT_cF$ effect observed at 1500 mg in the Caucasians (9.1–9.42 ms) was close to the threshold (10 ms) of regulatory concern whereas the corresponding predicted effect in the Japanese population dosed with the same dose was estimated to be much lower at 6.7 ms [58]. The outcome of the TQT study as positive or negative may be influenced by ethnicity for mild to moderate QT-prolonging drugs such as moxifloxacin. Given the potential size of the difference in effect, it seems paradoxical not to take account of the potential impact of ethnicity of the TQT study population when one considers the immense efforts frequently invested in aspiring to eliminate even smaller differences by very accurately measuring [59–61], extracting multiple ECGs and averaging them at each time point to minimize any errors arising from normal variability in QT_c interval [62] and appropriately correcting the QT interval for heart rate [63, 64].

Conclusions

Given all the regulatory guidance on addressing issues related to ethnicity, it seems extraordinary that during drug development, great attention is given to the influence of a whole range of demographic variables, ethnicity included, on the pharmacokinetics and clinical response in pivotal trials of a new drug and yet, when it comes to a major drug safety issue such as drug-induced QT prolongation, ethnicity seems to have attracted little attention. Hitherto, a vast majority of TQT studies have been conducted in Caucasians with poor enrolment of ethnic minority populations.

Increasingly, TQT studies are now conducted in non-Caucasian populations such as those in Asia or in Africa, largely as a means of reducing the otherwise exorbitant cost of a TQT study. The available information discussed above, however preliminary, collectively suggest that inter-ethnic differences in sensitivity to QT-prolonging drugs cannot be ruled out. At present, sponsors often provide subgroup analysis of TQT study data by gender. The time has now come for including subgroup analysis by ethnicity since subjects enrolled in a TQT study are not typically pre-genotyped and ethnicity is used as an all-inclusive surrogate of pharmacokinetic and/or pharmacodynamic variability between different populations.

Further adequately designed and powered studies, preferably TQT type studies, enrolling Caucasians, Oriental/Asian and African populations are needed to investigate

the pharmacologic properties and concentration–QT relationships of a few other drugs of different potencies before firm conclusions can be drawn. It also seems that E–R analysis is more efficient than changes in QT_c interval (ΔQT_c or $\Delta\Delta QT_c$) in unmasking ethnic differences (Tables 4 and 5) since the former, but not the latter, approach takes into account potential differences in exposure (dose and therefore, plasma concentrations).

In the immediate future, sponsors should consider investigating E–R relationship in domestic and foreign phase I and/or early phase II studies. Comparison of the two relationships should provide a better understanding of the extent to which data on drug effects on QT interval can be extrapolated from one population to another. Genetic analysis of outliers in these studies for mutations of ion channels and drug metabolizing enzymes will also greatly increase our understanding of inter-ethnic differences in QT liability of a drug.

If further definitive studies confirm that the QT-response in a Caucasian population is typically more intense than in a non-Caucasian population, the findings may have significant regulatory impact on domestic acceptance of TQT studies conducted in foreign populations. In broad terms, a TQT study undertaken in a Caucasian population may not need to be repeated in non-Caucasians. In contrast, a TQT study in a non-Caucasian population may well underestimate the intensity of QT effect in Caucasians. Regulatory decisions will of course have to be made on a case-by-case basis depending on a host of factors, not least the QT-prolonging potency of the drug and the anticipated differences in exposure in the domestic population. For drugs which are potent or only minimally active at prolonging the QT interval, ethnicity of the study population may matter little. However, drugs most likely to require individual attention with regard to ethnicity may be those with an effect close to the threshold of regulatory concern as defined in ICH E14. Whether these differences ultimately translate into differences in risk : benefit across different populations remains to be established.

Competing Interests

The author has completed the Unified Competing Interest form available at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares (a) no support from any organization for the submitted work and (b) no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. The author is the Director of a consultancy company which provides fee-earning advice to pharmaceutical companies on the design, conduct, analysis and interpretation of thorough QT studies.

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